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Coagulopathy in COVID-19 Infected Hospitalized Patients

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Abstract

Patients with severe COVID-19 are at increased risk of developing thrombotic events. The use of anticoagulants (AC) is recommended in all COVID19 infected hospitalized patients. There is controversy on the used dosage of anticoagulant and its survival benefit. Lower mortality was associated with high dose AC compared to medium or low dose AC. It was hypothesized that prolonged treatment with therapeutic dose of AC provides no survival benefit over prophylactic dose in severe COVID-19 patients admitted to the ICU.

Abbreviations: AC: Anticoagulants; IMPROVE: International Medical Prevention Registry on Venous Thromboembolism; VTE: Venous Thromboembolism; DVT: Deep Venous Thrombosis; PE: Pulmonary Embolism; DOACs: Direct Oral Anticoagulants; ICU: Intensive Care Unit

Introduction

Patients with severe COVID-19, caused by acute respiratory syndrome coronavirus 2 (SARS-CoV-2), are at increased risk of developing thrombotic events [1]. The incidence of thrombotic events in COVID-19 infected patients was largely drawn from data in patients with COVID-19 admitted to the intensive care unit (ICU) [2]. Thrombotic events were found in up to 69% of COVID-19 infected patients in the ICU [1]. VTE occurred in some ICU admitted cases despite receiving heparin prophylaxis and, even in the presence of therapeutic anticoagulation [2].

Several hypotheses can explain the underlying pathophysiology of the prothrombotic state occurring in COVID-19 infection. Hypercoagulability is mainly attributed to the combined effect of endothelial dysfunction and the exaggerated inflammatory response especially in those with severe disease. Other factors responsible for the development of a hypercoagulable state in these patients are COVID-19 associated hyperviscosity (greater than 95% of normal), inhibition of plasminogen system, platelet dysfunction [3], complement-mediated thrombogenesis, neutrophil activation with neutrophil extracellular traps formation resulting in widespread organ injury, and cytokine storm associated with severe COVID-19 infection. Antiphospholipid antibodies, especially lupus anticoagulant (LAC), may also contribute to hypercoagulability [3]. Coagulopathy is primarily driven by hypoxia [2]. Hypoxic conditions stimulate platelet and neutrophil adhesion to endothelial cells and tissue factor expression while suppress tissue factor pathway inhibitor and fibrinolytic pathways. NETosis is another robust mechanism for thrombus initiation by promoting platelet aggregation and coagulation activation. It is likely that each of these previously mentioned mechanisms plays a role, perhaps in tandem or in sequence [2].

VTE was present in about 20%–30% of these patients [3]. Arterial thromboembolism (ATE), VTE, DVT and PE were reported in 5%, 31%, 28% and 19%, respectively among SARS-COV-2 infected ICU patients [3]. Most of DVT were bilateral and affects the lower extremity. The VTE rate rises to 69% when surveillance ultrasonography was mandated. For this reason, it is recommended by one study to do mandatory ultrasonography on admission and repeat on day 7. The rates of proximal and distal thrombosis were not reported [2].

COVID-19 associated coagulopathy has distinctive laboratory features including elevated fibrinogen levels, modest thrombocytopenia, marked elevation in fibrin D-dimer values and prolongation of either prothrombin time [PT] or activated thromboplastin time [aPTT] [3]. The coagulopathy in COVID-19 differed from that of DIC in that fibrinogen levels are elevated,

thrombocytopenia is mild, and the PT is only slightly prolonged (1 to 2 seconds) [2]. There is no defined D-dimer threshold that can be used to diagnose thrombus non-invasively. High D-dimer level could not be used either to guide anticoagulant dosage or dose escalation. Non-survivor patients are more likely to have higher D-dimer and FDPs levels at the time of admission and a sharp decline in antithrombin levels as compared with survivors indicating their association with poorer prognosis in patients with coronavirus pneumonia and coagulopathy [3].

Anticoagulants and COVID-19

The use of anticoagulants (AC) is recommended in all COVID19 infected hospitalized patients [3]. The published guidelines are based on consensus statements and expert opinions only [3]. There is no universal consensus regarding the dosage, timing and duration of anticoagulation as well as the need for post discharge prophylaxis in COVID-19 hospitalized patients [3]. There is also controversy in the survival benefit of using anticoagulation. Lower mortality was associated with high dose AC compared to medium or low dose AC [1]. However, previous trials, showed no benefit from receiving intermediate-dose enoxaparin (1 mg/kg daily) as compared to standard dose thromboprophylactic enoxaparin (40 mg daily) in ICU admitted patients [4]. ICU patients requiring organ support (e.g., high-flow oxygen, invasive ventilation, vasopressor or inotropic support) did not experience benefit when receiving therapeutic intensity thromboprophylaxis (primarily low molecular weight heparin, LMWH) as compared to 'usual care' thromboprophylaxis (primarily LMWH) [4]. It was hypothesized that prolonged therapeutic dose of AC treatment provides no survival benefit over prophylactic dose AC in severe COVID-19 infected patients admitted to the ICU [1].

Summary of updated clinical recommendations

Updated clinical recommendations for thromboembolic prevention in COVID-19 infected hospitalized adult patients

i. Critically ill hospitalized patients are recommended to receive standard dose thromboprophylaxis instead of intermediate- or therapeutic intensity thromboprophylaxis [4].

ii. Non critically ill hospitalized patients are suggested to receive therapeutic intensity LMWH or UFH thromboprophylaxis if there is increased risk of disease progression or thromboembolism and the patients are not at high risk for anticoagulant related bleeding [4]. Direct oral anticoagulants have to be avoided when therapeutic intensity thromboprophylaxis is utilized [4].

iii. Patients are recommended to remain on the same intensity of VTE thromboprophylaxis initiated at hospital admission when transferred between floor to ICU for up to 14 days or until recovery as long as their bleeding risk is not significantly elevated [4].

iv. Standard dose thromboprophylaxis with LMWH or UFH is recommended in hospitalized patients incidentally found to have COVID-19 infection unless specific contraindications exist [4].

v. "Intermediate" intensity thromboprophylaxis and/or antiplatelet agents and/or statins are only used in the setting of a clinical trial on hospitalized COVID-19 infected patients [4].

vi. Clinical evidence supporting the use of serial D-dimer test to guide the intensity of antithrombotic therapy is lacking [4].

Post-hospital discharge thromboprophylaxis

a. Post-hospital discharge thromboprophylaxis is not routinely recommended in all COVID 19 infected patients, including those received therapeutic intensity anticoagulation thromboprophylaxis [4].

b. Candidates for post discharge thromboprophylaxis are patients at increased risk of thromboembolism (e.g., IMPROVE VTE score ≥4 or score 2–3 with elevated D-dimer) and not at increased risk of bleeding regardless of the intensity of their inpatient thromboprophylaxis [4].

c. Preferred DOACs include rivaroxaban (10 mg once a day) for 35 days [3].

d. Decisions regarding post discharge prophylactic anticoagulation should be individualized [3].

e. There is no role for routine measurement of D-dimer during post discharge follow-up [3].

f. DOACs do not require INR monitoring [3].

g. Clarification of the intended duration of post-hospital thromboprophylaxis is recommended to be illustrated to the treating health care providers to avoid unnecessarily prolonged exposure to anticoagulation [4]. Profuse glomerular hemorrhage and anticoagulant-related nephropathy (a form of acute kidney injury) linked to over-anticoagulation is not reported as a possible over-anticoagulation complication of COVID-19 among anticoagulated hospitalized patients [1]. There is a case report of GIT bleeding as a complication of oral anticoagulant in non-hospitalized COVID-19 infected patients who have no risk of thromboembolism [5].

Updated clinical recommendations for treatment of acute phase of venous thromboembolism

i. Patients should receive therapeutic intensity anticoagulation if there is acute deep vein thrombosis or pulmonary emboli or in patients who are at high risk of thrombosis and have predisposing risk factors such as old age, hypertension, diabetes or history of thromboembolic events [5]

ii. Initial therapy will include subcutaneous LMWH or UFH, with transition to DOAC therapy once the patient stabilizes prior to hospital discharge [4].

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iii. The duration of anticoagulation is determined according to the presence or absence of persistent risk factors and the patients' return to their baseline functional status [4].

iv. Most COVID-19 hospitalized patients with VTE and transient non-surgical risk factors such as medical illness are recommended to receive anticoagulation for a minimum of three to six months [4]. For secondary prevention, a finite course of anticoagulation (e.g., 3–6 months) rather than long-term continuing anticoagulation is suggested in most patients with COVID-19 associated VTE.

Vaccination in patients on anticoagulation or prior VTE/thrombophilia [4]

a. All patients with a history of thromboembolism, thrombophilia, or current use of anticoagulation are encouraged to receive COVID-19 vaccination.

b. Do not withhold anticoagulation for vaccine administration.

c. Prior history of VTE or current use of anticoagulant has no influence on the type of COVID-19 vaccine selected.

d. Pressure should be held for 5 min at the site of vaccine administration to minimize injection-related bleeding.

e. Standard warfarin monitoring schedules is not altered with vaccine administration in most patients. Those experience significant symptoms, such as fever or dietary disruption, should contact their treating doctor for any necessary additional INR follow up.

Conclusion

The published guidelines are based on consensus statements and expert opinions only. Therapeutic doses of heparin are recommended by the published guidelines only in diagnosed or highly suspected macrothrombi. There is no specific scoring system to assess VTE risk associated with COVID-19 on admission. There is no defined D-dimer threshold that can be used to diagnose thrombus non-invasively. High D-dimer level could not guide anticoagulant dosage or dose escalation. Post-hospital discharge thromboprophylaxis should not be generalized to all patients. Post discharge anticoagulants prophylaxis is recommended in all COVID-19 hospitalized patients at high risk of thromboembolism and not at increased risk of bleeding regardless of the intensity of their inpatient thromboprophylaxis.

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